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PATENT

REMARKS

Upon entry of this response, claims 1-6 and 8-12 will be pending. Claims 1 and 6 have been amended to include the feature "to a patient in need thereof". Amended claims 1 and 6 are fully supported by the specification at, for example, page 22, lines 5-18, which states: "A method for treating a skin disorder according to the present invention can comprise the step of local administration of a botulinum toxin to a patient with a skin disorder to thereby alleviate the skin disorder." New claim 12 is fully supported by the specification at, for example, page 1, lines 20-21, of the specification. No new matter is added.

As a preliminary matter, Applicant acknowledges the Office Action's comments regarding the missing two references: (CI) Bushara K., Otolaryngol Head Neck Surg 1996; 114(3):507; and (CM) Dugan et al. Mov Disord, 10(3);376:1995. Applicant is enclosing these references herewith.

Claims 1-6, 9 and 10 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,670,484 and EP 0 845 267 B1 (hereinafter "the Binder reference"). The Office Action alleges that disclosure of "lesion" by the Binder reference is the equivalent of the claimed "ulcer" feature. Applicant respectfully disagrees.

The type of "lesion" that the Binder reference discloses relates to cutaneous cell-proliferative disorders, e.g., psoriasis. A cutaneous cell-proliferative disorder is different from an ulcer. For example, a psoriasis lesion (a cutaneous cell-proliferative disorder) is "papules and plaques, sharply marginated with marked silvery-white scale". Exhibit 1: Color Atlas and Synopsis of Clinical Dermatology, Common and Serious Diseases, Fitzpatrick et al., McGraw-Hill, Inc., Second Edition (1992), page 40-41. On the other hand, an ulcer is "a skin defect in which there has been a loss of the epidermis and the upper papillary layer of the dermis". Exhibit 2: Id., at page 771. Thus, the "lesion" disclosed by the Binder reference is not an equivalent of the "ulcer" feature of the present claims. Accordingly, the claims are novel over the Binder reference.

Claims 6, 8 and 11 are newly rejected under 35 U.S.C. § 102(b) as allegedly being inherently anticipated by the Binder reference (U.S. Patent No. 5,670,484). Specifically, the Office Action alleges that the Binder reference "has the same method steps and the same end point as that of the Applicant. [Therefore, it] would inherently treat warts." The Office Action at page 7. Applicant respectfully asserts that the Office Action has misapplied the law of inherency. The MPEP §2112 (IV) states:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

(emphasis in original). Further, the MPEP §2112 (IV) states:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)...

(emphasis added). The claims are directed to the administration of botulinum toxin to treat a particular skin disorder that has been diagnosed/identified, and the claims have been amended to recite "a patient in need thereof" to clarify this feature. **Accordingly, the claimed invention requires a step of diagnosing/identifying a patient with a specific skin disorder (i.e., warts) and administering botulinum toxin to treat that skin disorder.** The Binder reference does not disclose the step of diagnosing/identifying a patient with warts and thereby administering botulinum toxin to treat the warts. Further, the step of diagnosing/identifying a patient with warts and thereby administering botulinum toxin to treat the warts does not necessarily flow from the teachings of the Binder reference, which teaches administering botulinum toxin to treat the cutaneous cell-proliferative disorder (i.e., psoriasis lesion and dermatitis lesion).

Claim 11 is newly rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent Application Publication 2004/0087893 A1 (hereinafter "the Kwon reference"). The Office Action alleges that the Kwon reference discloses a method of administering a botulinum toxin for treating warts at page 6, section 0077.

Contrary to this allegation, the Kwon reference does not disclose a method of administering a botulinum toxin for treating warts. The Kwon reference discloses a solid drug solution perforator (SSP) system and an associated drug reservoir for delivering therapeutic, prophylactic and/or cosmetic compounds, for nutrient delivery and for drug targeting. With regard to page 6, section 0077, of the Kwon reference, it reads:

> Another area of applications is cosmeceutical. An SSP system including a patch can deliver botox toxin or a hydroxyacid more efficiently and safely to remove or reduce wrinkle formation and skin aging. The system is also useful for treating lesions or abnormal skin features, such as pimples, corns, warts, calluses, bunions, actinic keratoses and hard hyperkeratotic skin, which is often found on the face, arms, legs or feet.

As such, the Kwon reference teaches that botulinum toxin can be delivered by the SSP system. However, the Kwon reference only teaches that botulinum toxin can be delivered by the SSP system "to remove or reduce wrinkle formation and skin aging." **The Kwon reference does not teach or suggest that botulinum toxin may be administered to treat warts.** In fact, the Kwon reference does not teach the use of any drug to treat warts. At most, the Kwon reference teaches that a medication known for treating warts (which does not include botulinum toxin) may be delivered by the SSP system to treat warts. Thus, the Kwon reference cannot anticipate the claimed inventions.

The Office Action also alleges that the Kwon reference inherently discloses a method of administering a botulinum toxin for treating warts. However, the Office Action has not established that the method of administering a botulinum toxin to treat warts *necessarily flows* from the teaching of the Kwon reference. The Kwon reference only teaches that the claimed SSP system may be used in combination with botulinum toxin to reduce wrinkle formation and skin aging. With regard to warts, the Kwon reference merely suggests that the claimed perforator system may be used in combination

with a drug to treat warts. Perhaps the Office Action is suggesting that there is a **probability or possibility** that the claimed perforator system may be used in combination with a botulinum toxin to treat warts. In this respect, Applicant respectfully directs the Office to the MPEP sections sited above, which states that inherency may not be established by probabilities or possibilities. The claimed method of administering a botulinum toxin to treat warts must *necessarily flows* from the teaching of the Kwon reference—which it does not. Accordingly, the Office Action has not met the requirements for establishing that the Kwon reference inherently anticipates the claimed invention. Thus, the claimed invention is novel over the Kwon reference.

In view of the foregoing, Applicant submits that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

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Botulinum Toxin and Rhinorrhea

To the Editor:

I read with great interest the results of Shaari et al.'s study.[1] Using a dog model, they demonstrated that topical application of botulinum toxin type A to the nasal mucosa inhibits nerve-evoked secretions.[1] These results offer yet another therapeutic potential for botulinum toxin, as an alternative treatment in vasomotor rhinitis.

The authors proposed the injection of the sphenopalatine ganglion as a more effective way of delivering the toxin to the nasal glands. Direct submucosal injection of botulinum toxin is likely to produce more control of mucosal secretions. The injected dose is likely to spread locally, producing a field of selective denervation of the nasal seromucinous glands. The size of this regional denervation field is proportional to the dose injected. From our studies using subcutaneous injections of botulinum toxin to block the cholinergic sympathetic fibers to sweat glands, we found that one-point injection of 20 U of (Dysport-Porton Products, U.K.) in the dorsum of the hand produces a circular area of complete anhidrosis 5 to 6 cm in diameter.[2,3] Unlike the proposed sphenopalatine injections, direct submucosal injections are less likely to produce dry eyes.

Of the four dogs studied, one had a paradoxical response with increased secretions. Although this can be attributed to inadequate stimulation of the control side or failure of the toxin to penetrate the mucosa, a "true paradoxical effect" of the toxin cannot be ruled out.[4] Excessive salivation has been known to occur in botulism.[5] A similar paradoxical effect on lacrimal glands, producing watering of the eyes, has been reported in patients receiving periorbital injections for blepharospasm or hemifacial spasm.[6] The paradoxical effect of the toxin on the "neuroglandular junction" remains unexplained.[4] It may represent hypersensitivity of the denervated glands in a similar fashion to the well-known phenomenon of "paralytic secretion," in which excessive salivation occurs a few days after denervation of the salivary glands and persists for 2 to 3 weeks.[7] The autonomic dysfunction in botulism out lasts skeletal muscle paralysis, indicating that the neuroglandular junctions require more time to recover. This has been our experience with botulinum toxin–induced anhidrosis, an effect that may last up to 11 months (Bushara, Unpublished observation, 1995).

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Autoimmune Inner Ear Disease

I could not let the *Letter to the Editor* that appeared in The JOURNAL (Boyles JH Jr, 1995;112:631-3) go without comment. It was difficult to believe the author had not removed his blinders and failed to site the literature of current investigation by Harris[1-14] and Mosciki[15-19] and previous articles by McCabe.[20-23] No one refutes the possible role of allergy in fluctuating sensorineural hearing loss. But, get real; if one is going to stand on a publishing soap box and spout disparaging statements about others and then tout one's own philosophies without the facts, that's bad journalism.

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The effect of botulinum neurotoxin-B on insulin release from a β-cell line

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The identification of a non-neuronal homologue of synaptobrevin, cellubrevin, in which the Botulinum neurotoxin-B (BoNT-B) sensitive proteolytic cleavage site is conserved, raises the possibility that secretions from cells other than neuroendocrine cells may be sensitive to inhibition by BoNT-B. Secretion from such cells is not normally subject to inhibition by BoNT-B due to a highly selective uptake mechanism present only on the presynaptic terminals of the neuromuscular junction. The insulin secreting cell line HIT-15 is derived from pancreatic β cells. Pancreatic cells are of endoderm origin. We have studied the effects of BoNT-B on HIT-15 cells following introduction of the toxin into the cell cytosol by electroporation. In control cells, potassium (30mM) stimulated insulin release from 17.4 +/- 1.8 ng of insulin/h/mg of protein to 61.9 +/- 8.8 ng of insulin/h/mg of protein. By contrast, in BoNT-B treated cells, potassium only stimulated insulin release from 19.2 +/- 4.8 ng of insulin/h/mg of protein to 33.7 +/- 3.3 ng of insulin/h/mg of protein. The inhibition of potassium stimulated insulin release in cells pre-treated with BoNT-B was significant (n=6, p<0.05). Western blot analysis indicated that the HIT-15 cells contained two proteins reactive with an anti-synaptobrevin/cellubrevin antibody. Analysis of these proteins by Western blot in extracts from the cells where inhibition of insulin secretion by BoNT-B had been observed, showed reduced levels of reactivity. Thus BoNT-B appears to inhibit insulin secretion from HIT-15 cells by cleaving synaptobrevin/cellubrevin in these cells. These results suggest that pancreatic β-cells contain an isoform(s) of synaptobrevin which is involved in the secretion of insulin, thus making insulin secretion in these cells sensitive to inhibition by botulinum neurotoxin B.

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The insulin secreting β-cell line, HIT-15, contains SNAP-25 which is a target for botulinum neurotoxin-A

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The mechanism of action by which botulinum neurotoxin-A (BoNT-A) inhibits acetylcholine release at the neuromuscular junction has recently been reported to be proteolytic cleavage of the neuronal protein SNAP-25, synaptosomal-associated protein of 25 kDa. Independently, SNAP-25 has been proposed to be a component of a fusion complex involved in both neuronal and non-neuronal exocytotic fusion events. The possibility, therefore, exists that SNAP-25, or homologues, will be found to play a role in exocytotic fusion events other than neurosecretion. Analysis of the hydrophobic protein fraction of the insulin secreting β-cell line, HIT-15, by Western blot revealed the presence of a SNAP-25 immunoreactive protein of approximately 25 kDa. Electroporation of BoNT-A into the HIT-15 cell resulted in loss of this immunoreactive band indicating proteolytic cleavage. This is highly suggestive that the HIT-15 cell contains SNAP-25 or a close homologue. Furthermore, cells into which BoNT-A had been electroporated displayed a significantly (P < 0.001, n = 10) inhibited secretion of insulin in response to a potassium-depolarisation stimulus. In control cells a potassium-depolarization stimulus (30mM) stimulated insulin release from 18.0 +/- 2.7 ng/h/mg of protein to 51.1 +/- 0.9 ng/h/mg of protein, whilst in cells treated with BoNT-A the potassium-depolarization stimulus stimulated release from 18.0 +/- 4.6 ng/h/mg of protein to 21.4 +/- 5.3 ng/h/mg of protein. These results show that the pancreatic β-cell derived HIT-15 cell contains a substrate for botulinum neurotoxin-A, and that this renders them sensitive to inhibition of insulin secretion by the neurotoxin.

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A survey of botulinum neurotoxin substrate expression in cells.

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Botulinum neurotoxins (BoNtx) are known to be zinc-dependent proteases specific for one of three presynaptic proteins: synaptobrevin (serotypes B,D,F and G), syntaxin 1 (C1), or SNAP-25 (A and E). Non-neuronal isoforms of the first two of these have been discovered (cellubrevin and syntaxins 2-5); of these cellubrevin has been shown to be a substrate for BoNtx B,D,F and G. It has been suggested that these proteins form complexes that may be ubiquitously involved in membrane-membrane fusion events.

Using a panel of antibodies we have screened a large number of cell types, from both immortalized cell lines and primary cultures, for the presence of the known substrates for the BoNtx. While SNAP-25 and syntaxin were found only in cells of a neuroendocrine lineage (e.g. chromaffin cells, PC12, GH3, and insulinomas) both cellubrevin and synaptobrevin were detected in all cell types tested, from fibroblasts (e.g. BHK) to myeloid cells (e.g. mast cells). It was notable, however, that the neuroendocrine-derived cells contained more synaptobrevin than cellubrevin, while others (e.g. fibroblasts) contained a greater proportion of cellubrevin. Preliminary data from RT-PCR studies has confirmed the expression pattern of these gene products in a number of cell types.

These data provide some evidence for the existence of a universal mechanism for membrane fusion events, although the target membrane partners for synaptobrevin and cellubrevin (presumably syntaxins 2-5) remain to be identified in the non-neuroendocrine cell types.

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ARE THE PARAMETERS OF BLINK REFLEX GOOD OBJECTIVE MEASURES FOR THE PERIPHERAL EFFECTS OF BTX-A?

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OBJECTIVE: To evaluate the potential use of the parameters of Blink reflex as objective measures for the peripheral effects of BTX-A.

BACKGROUND: There is no objective method to evaluate the pharmacological effects of BTX-A in patients. The Blink Reflex(BR) was used before as a tool to elicit brain stem abnormalities in cranio-cervical dystonic patients. However different authors showed changes in the characteristics of both responses R1 and R2 of BR.

METHODS: Twelve sequential " never treated before" patients with the diagnosis of Blepharospasm or Hemifacial spasm were studied. The BR were recorded at baseline and at 1 month after the treatment with BTX-A. At the same visits the evaluations of the clinical severity of the disease were done using the Tolosa rating scale and the subjective assessment by the patient. All reported or observed adverse reactions were also recorded.

The BR was recorded according the following protocol: [illegible] stimulus were used initially with increasing steps of 1 mA to define the threshold in each side - minimum intensity to obtain stable responses with repeated trials. After threshold definition the intensity was increased by 50% above threshold in order to obtain stable maximal responses. After each stimulation three latencies times were measured: from stimulus artifact to the initial deflection of R1; to the earliest deflection of the ipsilateral R2; to the earliest deflection of the contralateral R2.

RESULTS: Ten patients have blepharospasm and 2 patients have Hemifacial spasm. The table summarizes the data concerning the patients with blepharospasm who had clinical improvements that ranged from 0%(1 patient) to 100%(3 patients). The threshold (T) is highly different after the treatment with BTX-A (paired t student - p <0.0019).The latencies measured are remarkably stable across the study. The amplitude of R1 is significantly reduced after the treatment.

T before BTX-A	T after BTX-A		Right R1 before BTX-A	Right R1 after BTX-A	Right ipsiR2 before BTX-A	Right ipsiR2 after BTX-A	Right contR2 before BTX-A	Right contR2 after BTX-A
6.96	28.30	Lat. mean (msec)	12.11	12.32	38.04	38.86	40.82	40.53
4.38	12.58	Lat. sd	1.30	1.46	4.34	3.36	4.92	40.39
		Amplitude mean (µV)	260.87	73.76				
		Amplitude sd	166.38	23.87				

DISCUSSION: Our preliminary data showed that the latencies of the responses of BR are not changed by the treatment with BTX-A when a clear supramaximal stimulus is used in each record. However in these experimental conditions-supramaximal stimulation- the amplitude of the R1 response is clearly reduced. Therefore we may conclude that when there is a reduction in the amplitude of the R1 response the treatment with BTX-A had produced its pharmacological effect whether or not a therapeutic effect had been verified. Further work is need to find out if there is a cut-off point from where further reduction in the amplitude are not followed by greater clinical improvement.